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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/322,289	SCHENK, DALE B.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-8,10-12,17,21-28,31-58,60-90 and 93-102* is/are pending in the application.

4a) Of the above claim(s) *25-28,33,34,38-58 and 60-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,10-12,17,21-24,31,32,35-37,82-90 and 93-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1,2,4,6-8,10-12,17,21-28,31-58,60-90 and 93-102.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4/16/07, 4/19/07, 4/25/07,5/7/07,6/27/07.

DETAILED ACTION

1. The remarks and amendments filed 16 April 2007 have been entered. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 28, 31 – 58, 60 – 90, and 93 – 102 are pending.

Election/Restrictions

2. Claims 25 – 28, 33 – 34, 38 – 58, and 60 – 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 19 December 2000.

3. This application contains claims 25 – 28, 33 – 34, 38 – 58, and 60 – 81 drawn to an invention nonelected with traverse in the reply filed on 19 December 2000. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are under examination.

Withdrawn Rejections and Objections

5. The following rejections and objections set forth in the previous office action are withdrawn:

A. The objection to claim 1 is withdrawn in light of the amendments which delete redundant language.

B. The rejection under 35 USC 112, second paragraph is withdrawn in light of the amendments to independent claims 1 and 82, which clarify the scope of the claims.

C. The rejection of claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, and 35 – 37 under 35 USC 112, first paragraph for lack of enablement commensurate in scope with the claims is withdrawn in light of the arguments presented. The examiner concedes that the specification provides a disclosure that is sufficient to enable the skilled artisan to practice the claimed methods of treating disease without resorting to undue experimentation. However, the rejection of claims 82 – 90 and 93 – 102 for lack of enablement commensurate in scope with the claims stands as explained below.

D. The rejections under 35 USC 102(b) are withdrawn in light of the amendments. The claims now require administration of antibodies which are of isotype IgG1. This limitation is not taught by Becker (EP 0 613 007) or by Anderson (US 5,589,154).

E. The rejections of record under 35 USC § 103 are withdrawn. The references cited do not explicitly teach administration of IgG1 antibodies, which is now required by all claims.

F. The provisional double patenting rejections over 10/704,070, 10/703,713, 10/923,267 are moot as these applications have been abandoned.

Information Disclosure Statement

6. The information disclosure statements filed 16, 19, 25 April 2007, 7 May 2007 and 27 June 2007 have been considered. On the IDS filed 16 April 2007, reference 790 has been crossed off as there is no date thus the examiner cannot determine if the reference constitutes prior art.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 82 – 90 and 93 – 102 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of antibodies which specifically bind Aβ protein, does not reasonably provide enablement for prophylaxis of disease as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of

experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

This rejection stands for the reasons of record. Briefly, the claims are drawn to prophylaxis of disease characterized by an amyloid depositing which contains Ab peptide. The definition of prophylaxis set forth at p. 27 of the specification clearly states that the scope of this term includes elimination of the risk of disease. That is, the claim encompasses complete prevention of disease and total elimination of any possibility of ever coming down with the disease. The specification discloses that treatment with anti-Aβ antibodies decreases the number of plaques, it does not disclose prevention of all symptoms.

The specification discloses the results of experiments in which PDAPP transgenic mice received Aβ injections (see p. 36; while this section of the specification is on point to administration of protein rather than antibodies, since this protein elicits an antibody response and the antibodies themselves are therapeutic (pp. 70 – 72), it is reasonable that the effects of antibodies would be similar); seven of nine tested mice had no Aβ deposits in the brain (p. 38). The two other mice, however, did have some amyloid plaques. Clearly, while administration of Aβ peptide elicited antibodies and reduced the prevalence of amyloid deposits, it failed to totally eliminate the risk of disease, as evidenced by the two mice (22% of tested subjects) who still have amyloid deposits. Thus while the specification shows actual reduction to practice of delaying onset of disease and decreasing severity of plaque burden in animals that receive Aβ injections (and would reasonably be expected to show a similar result for animals that receive Aβ antibodies), there are no working examples of complete elimination of risk of disease.

Additionally, the mouse model presented is not a physiologically relevant model for prevention of disease in a normal, healthy person. The PDAPP mice are transgenic mice which overexpress a mutated form of Aβ that renders them likely to develop Alzheimer's-like pathology (specification, p. 36). These mice produce an excessive amount of the mutated form of the protein from birth. They are not physiologically normal and do not realistically reflect physiology in normal, asymptomatic subjects. If the antibodies are effective in reducing the severity or delaying onset of disease as applicant hypothesizes, i.e. by binding to Aβ protein and clearing it from neurons, the most parsimonious explanation for the observed effects would be that the antibodies bring the concentration of Aβ protein back into its normal physiological range and out of the abnormally high ranges that had been present throughout the animal's life. It is improper

to conclude, based upon the data presented in the specification, that decreasing Aβ concentration in normal healthy subjects is desirable. All that one can conclude is that decreasing excessive levels of mutated Aβ protein is desirable.

The skilled artisan would recognize that administration of antibodies against Aβ would be likely to have deleterious effects in normal healthy patients. While it is clear that over-expression of mutated forms of Aβ protein can lead to symptoms not unlike those seen in Alzheimer's disease, this does not indicate that the levels of the protein should be suppressed in healthy patients. Aβ protein has an important physiological role in normal, healthy mammals. Liu et al. (1998. Proc Natl Acad Sci USA 95:13266-13271) teach that Aβ protein is important in regulating cholesterol homeostasis. Perez et al. (1997. J Neurosci 17:9407-9414) teach that β-amyloid precursor protein (also known as APP, from which Aβ protein is cleaved) is important for neuronal viability and axonal outgrowth, and that secretory products of APP "modulate axon growth, dendrite branching, and dendrite numbers" (abstract). Thus the skilled artisan would immediately understand that administration of antibodies against Aβ protein would most likely be deleterious to a normal healthy subject. Not only does the specification fail to provide working examples of elimination of risk of disease, but also fails to provide evidence that decreasing Aβ protein levels in normal individuals is healthy or even desirable. The state of the art indicates that one would not want to disrupt the levels of Aβ protein in normal, healthy individuals.

The instant situation is quite different from the delivery of vaccines on a prophylactic basis. When vaccines against foreign pathogens are delivered, antibodies are made and B-cells are activated; this can prove effective in mitigating subsequent infections with the same pathogen. Importantly, there is no disruption of the vaccinated individual's normal physiology, as the antibodies against the pathogen have no effect on endogenous proteins. In contrast, when antibodies against Aβ protein are delivered, or when Aβ protein itself is administered as a vaccine, the antibodies would be expected to impair cholesterol homeostasis and modulate neuronal growth and dendritic arborization, as the antibodies would bind to endogenous Aβ protein.

At pp. 12 – 13 of the remarks filed 16 April 2007, applicant cites several cases including *In re Cortright* and *Ex Parte Saito*, and argues that the standard being applied by the examiner is beyond that which is required by the law. Applicant argues that the mere presence of some difficult-to-achieve embodiments within the scope of the claim does not render the claim non-

enabled. Applicant's arguments have been fully considered but they are not persuasive. The examiner has set forth sound scientific reasons as to why the art indicates administering antibodies that bind to Aβ protein would not be efficacious: PDAPP mice are not a reasonable model for prevention of disease, owing to their abnormally high levels of expression of mutated Aβ protein; thus the animal model used in the specification is not predictive of prophylaxis in unaffected individuals. The examiner has set forth sound scientific reasons as to why administering antibodies that bind to Aβ protein would not even be desirable: doing so would disrupt the normal physiology of unaffected subjects. The specification fails to set forth working examples of complete elimination of risk, which is encompassed by the full breadth of the claims. The prior art indicates that these are serious problems which the specification as filed fails to overcome. While the presence of inoperative subject matter within a claim does not necessarily render the claim non-enabled, as the degree of non-enabled subject matter increases the balance tips away from enablement and towards non-enablement; see MPEP § 2164.08(b). Thus the rejection of claims 82 – 90 and 93 – 102 stands for the reasons of record.

Double Patenting

8. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 19 of U.S. Patent No. 6,743,427. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

9. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 36 of U.S. Patent No. 6,761,888. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ. Note that the issued claims encompass

therapeutic and prophylactic treatment, (see claim 1), administration of human IgG1 antibodies (claim 19), as well as humanized (claim 14), chimeric (claim 15), and monoclonal antibodies (claim 17).

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

10. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 38 of U.S. Patent No. 6,913,745. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope; the issued claims of the '745 patent are limited to administration of specific humanized antibodies whereas the instant claims are generic with respect to which antibodies are to be administered. Note that the issued claims encompass humanized (claims 12, 31), monoclonal (claims 16 and 35), and chimeric antibodies (claims 14 and 33).

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

11. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56 – 195 of copending Application No. 10/828548. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case they encompass administration of antibodies which bind to Aβ protein for treatment or prevention of Alzheimer's disease. Note that in the '548 case claims 69, 83, 100, 108, and 112, amongst many others specifically encompasses monoclonal, humanized, and chimeric antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

12. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 133 – 136 of copending Application No. 10/232030. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '030 case they are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

13. Claims1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 52, 54 – 94, 138 – 163 of copending Application No. 10/923469. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the '469 case some claims are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

14. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 46 of copending Application No. 10/890071. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the antibodies to be administered can bind to any epitope whereas in the other case the claims are limited to specific epitopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Kuby (1997. Immunology, Third Edition, p. 123, cited in office action mailed 17 November 2006) and Adair et al. (WO 91/16928, cited in office action mailed 17 November 2006).

Becker teaches administration of antibodies which bind to Aβ protein for treatment of Alzheimer's disease (see column 7 lines 44 – 52). Becker's antibodies include chimeric and humanized antibodies (see column 5 lines 50 – 58), which is on point to claims 1 and 11 – 12 as well as monoclonal antibodies, which are on point to claim 10. Note that the reference specifically teaches administration to humans for treatment of Alzheimer's (column 7), which is on point to claims 1 – 2 and 4. While claim 1 recites "a regime effective to ... treat the disease", no particular doses are recited within the claim and since the prior art reference teaches treatment, it is presumed to be "effective". Becker also teaches administration in pharmaceutical compositions further comprising carriers (see column 8 lines 19 – 42, which is on point to claim 24). The reference teaches that the antibodies are specific for Aβ protein in a β-sheet conformation (see column 5 lines 42 – 50), which is on point to claim 31 and further teaches that the protein only adopts this conformation after aging of the peptide in culture medium or water for at least 1 days (see paragraph spanning columns 2 – 3), therefore the antibodies which bind Aβ in β sheets would not be expected to bind full-length APP.

Additionally Becker teaches administration routes including intravenous (see column 8), which is on point to claim 32. However Becker does not explicitly teach administration of antibodies of isotype IgG1 as recited in claim 1, does not explicitly teach administration of human monoclonal antibodies as encompassed by claim 10 and does not teach the specific doses recited in claims 22 – 23 or the duration of administration as recited in claim 36.

Kuby teaches the structure of human IgG isotypes and teaches that they vary in size and in the structure of the hinge region. Kuby teaches that IgG1 is the most prevalent of the four IgG subclasses (see paragraph spanning the two columns of p. 123) and further teaches that the subtle differences in amino acid sequences between the various IgG classes lead to differences in the hinge region, and that these subtle difference also lead to differences in biological activities of the various classes of IgG isotypes (p. 123 second column first complete paragraph). Finally Kuby teaches that the classes (or isotypes) are determined not by the antigen binding region but by the constant region, which remains constant for any given isotype independent of the antigen bound. However while Kuby describes the particular IgG isotypes she does not provide guidance for selection of IgG1 in particular and does not teach administration of antibodies that bind to Aβ protein as recited in claim 1.

Adair teaches that the binding affinity of humanized antibodies which bind to ICAM-1 varies with isotype. Adair teaches that IgG1 isotype binds more strongly than other isotypes, and this is due to the structure of the hinge and constant regions of IgG1, providing motivation to the artisan of ordinary skill to select IgG1 antibodies based on their strong ability to bind to antigens. See especially pp. 22 – 23. However Adair does not teach administration of antibodies that bind to Aβ protein as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of administering antibodies which bind to Aβ protein for treatment of Alzheimer's disease taught by Becker to specifically include the antibodies of IgG1 isotype taught by Kuby and Adair. The motivation to do so would be to select antibodies that bind tightly to the target antigen; this motivation flows directly from the prior art references themselves. Becker teaches that the treatment with antibodies is efficacious; Adair teaches that antibodies of IgG1 isotype bind to antigens very well, and Kuby teaches that the biological properties of the specific isotypes is dependent upon the structure of the constant region, not the variable (antigen-binding) domain.

Although Becker does not explicitly teach selection of a human monoclonal antibody of isotype IgG1 as encompassed by claim 10, doing so would be obvious to the artisan of ordinary

skill. Selecting a human monoclonal antibody would be advantageous, as this antibody would elicit a decreased immune reaction, particularly as compared to a mouse antibody. Note that Becker discusses the need to humanize antibodies (column 6 line 31 – column 7 line 10) and describes production of monoclonal antibodies as well-known in the art (column 6 line 10). Thus selecting a human monoclonal antibody of isotype IgG1 would have been obvious to one of ordinary skill in the art, particularly in light of the Becker reference which teaches the need to minimize immune rejection and teaches administration to humans.

It would have been obvious to one of ordinary skill in the art to modify the method of Becker by adjusting the dose or duration of the administration protocol, with a reasonable expectation of success. The motivation to do so would be to more effectively treat Alzheimer's disease. See MPEP § 2144.05(II), which states that optimization of conditions through routine experimentation is not considered a contribution over the prior art and thus rejections under 35 USC § 103 are appropriate.

On p. 14 of the remarks filed 16 April 2007, applicant argues that "any allegation in the next office action that rejection of these claims [claims 10 and 88] was necessitated by applicant's amendment would be incorrect", as the only reasonable interpretation of claim 10 was that it limited the method of administering antibodies of claim 1 to human monoclonal antibodies of isotype IgG1. Applicant argues that since claim 1, prior to this amendment, read "...or a human monoclonal antibody and the antibody is of isotype human IgG1", claim 10 necessarily limited claim 1 to administration of human monoclonal IgG1 antibodies, and that this limitation was not addressed by the examiner in the previous office action. Applicant's arguments have been fully considered but they are not persuasive. Claim 1, as previously presented, was very confusing. It was unclear whether the limitation "the antibody is of isotype human IgG1" referred to "a human monoclonal antibody" which immediately preceded such language or to "wherein the antibody is a chimeric or humanized antibody", which occurred earlier but used the same definite article. The recitation "the antibody" lacked definite antecedent basis as there were multiple recitations of "antibody" at various points in the claim before the recitation of "the antibody". As claim 1 now very clearly requires that any of the antibodies administered be human IgG1 isotype, the inclusion of claim 10 in this rejection was in fact necessitated by applicant's amendment.

16. Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 35 – 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 above, and further in view of Miller (U.S. Patent 5,227,159 (of record).

The reasons why the references by Becker, Kuby, and Adair render obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 - 32, and 36 are set forth above. However none of these references teaches monitoring the patient for antibody levels as recited in claim 35.

Miller teaches administration of anti-HIV antibodies for treatment of disease. Miller also teaches measuring the levels of antibodies and repeating administration of the antibody as indicated by the circulating antibody levels (see column 15 lines 52 - 62), which is on point to claim 35. However Miller does not teach treatment of Alzheimer's disease by administration of antibodies which bind Aβ.

It would have been obvious to monitor antibody levels as taught by Miller, when treating Alzheimer's disease by administering antibodies that bind to Aβ protein as taught by Becker. The motivation to do so would be to optimize the circulating level of antibody, thereby ensuring that a therapeutic dose was maintained.

17. Claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 – 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 above, and further in view of Sabel (U.S. Patent 4,883,666, of record).

The reasons why the references by Becker, Kuby, and Adair render obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31, - 32, and 36 are set forth above. However none of these references teaches sustained release compositions as recited in claim 37.

Sabel teaches implantation of controlled release systems for treatment of neurological diseases (see column 10 - column 12). Sabel teaches the implants are suitable for administration to patients with Alzheimer's disease (column 5 lines 5 - 26). However Sabel does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to implant a controlled release system to administer the antibodies, as taught by Sabel, with a reasonable expectation of success. Sabel teaches there are many advantages to implantation of controlled release systems, including constant predictable release and local administration, thereby obviating the

need for high systemic doses (see column 2 lines 49 - 65).

18. Claims 1 – 2, 4, 6 – 8, 10 – 12, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 above, and further in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342, of record).

The reasons why the references by Becker, Kuby, and Adair render obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 - 32, and 36 are set forth above. However none of these references teaches administering to patients under 50, as recited in claim 6, or patients with either inherited (claim 7) or no known (claim 8) risk factors.

Brookmeyer teaches that the incidence of Alzheimer's disease increases as people age, and further teaches that delaying onset or reducing severity even slightly would result in enormous savings, given the expected financial burden of the disease and the increasing percentage of the population that will live to old age. However Brookmeyer does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to use the method of Becker to treat patients under 50, or patients either with or without known risk factors, with a reasonable expectation of success. The motivation to do so would be to delay the onset of the disease, which would result in considerable savings.

19. Claims 1 – 2, 4, 10 – 12, 17, 22 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 above, and further in view of Yachi (EP 0 285 159, of record).

The reasons why the references by Becker, Kuby, and Adair render obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31 - 32, and 36 are set forth above. However none of these references teaches administering a second antibody that binds to amyloid deposit as recited in claim 17.

Yachi teaches a second antibody that binds to Aβ protein. However Yachi does not teach administration for treatment of disease.

It would have been obvious to one of ordinary skill in the art to co-administer the antibodies from Becker and Yachi, with a reasonable expectation of success. It is *prima facie* obvious to co-administer two compounds known to be suitable for the same purpose (MPEP §

2144). Becker and Yachi teach antibodies that bind Aβ, and Becker teaches they are suitable for treatment of Alzheimer's.

20. Claims 1 – 2, 4, 10 – 12, 21 – 24, 31 – 32, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 – 2, 4, 10 – 12, 22 – 24, 31 – 32, and 36 above, and further in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

The reasons why the references by Becker, Kuby, and Adair render obvious claims 1 – 2, 4, 10 – 12, 22 – 24, 31, - 32, and 36 are set forth above. However none of these references teaches heterologous peptides fused to the antibodies as recited in claim 21.

Zhang et al. teach labeling by epitope-tagging for detection of molecules. It would have been obvious to one of ordinary skill in the art to epitope tag the antibody of Becker, as taught by Zhang et al., with a reasonable expectation of success. A motivation to do so would be to detect the antibody in a heterogeneous sample. Becker teaches that their antibodies are useful for detection in diagnostic assays (see column 7). Because these are heterogenous samples using a labeled antibody as taught by Zhang is particularly useful, as the epitope allows for easy detection.

21. Claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, of record) in view of Kuby (1997. Immunology, Third Edition, p. 123, cited in office action mailed 17 November 2006) and Adair et al. (WO 91/16928, cited in office action mailed 17 November 2006).

Claim 82 and dependent claims encompass administration to patients displaying no symptoms of the disease, as they are drawn to prophylaxis and merely require administration to "a patient", i.e. any patient and includes patients with no known risk factors for the disease (see for example dependent claim 87). Anderson teaches administration of antibodies which bind to Aβ; see column 16 lines 35 – 40 for example. Note that the antibodies of the invention can be humanized as recited in claim 82, and that Anderson specifically teaches the artisan how to make humanized antibodies (see column 12 lines 10 – 49). As set forth previously, all patients are at risk of developing Alzheimer's disease. Thus the reference by Anderson is on point to claims 82 – 83, which encompass administration of antibodies that bind Aβ to patients at risk of,

but not yet having, Alzheimer's. Anderson also teaches administration to humans (see for example column 16 which discloses that human serum albumin is to be included, and also discloses treatment by paramedics and emergency room attendants, which is clearly directed to humans), which is on point to claim 84. The reference teaches administration to patients with cerebral hemorrhage, but not to patients with known risk factors of Alzheimer's disease, which is on point to claim 87. Anderson teaches administration of humanized antibodies, which are a form of chimeric antibodies, and are on point to claims 89 – 90. Anderson teaches pharmaceutical compositions (see column 15 line 65 – column 16 line 34), which is on point to claim 97. The antibodies are disclosed to be specific for Aβ and would not be expected to bind to full-length APP, which is on point to claim 98. Anderson teaches administration via IV infusion (see column 16 lines 38 – 40), which is on point to claim 99, as well as sustained release compositions comprising the antibody are also suitable for administration (see column 16 lines 12 – 34), which is on point to claim 102. However Anderson does not explicitly teach administration of antibodies of isotype IgG1 as recited in claim 82 and does not teach the particular doses recited in claims 95 – 96 and duration recited in claim 101.

Kuby teaches the structure of human IgG isotypes and teaches that they vary in size and in the structure of the hinge region. Kuby teaches that IgG1 is the most prevalent of the four IgG subclasses (see paragraph spanning the two columns of p. 123) and further teaches that the subtle differences in amino acid sequences between the various IgG classes lead to differences in the hinge region, and that these subtle difference also lead to differences in biological activities of the various classes of IgG isotypes (p. 123 second column first complete paragraph). Finally Kuby teaches that the classes (or isotypes) are determined not by the antigen binding region but by the constant region, which remains constant for any given isotype independent of the antigen bound. However while Kuby describes the particular IgG isotypes she does not provide guidance for selection of IgG1 in particular and does not teach administration of antibodies that bind to Aβ protein as recited in claim 1.

Adair teaches that the binding affinity of humanized antibodies which bind to ICAM-1 varies with isotype. Adair teaches that IgG1 isotype binds more strongly than other isotypes, and this is due to the structure of the hinge and constant regions of IgG1, providing motivation to the artisan of ordinary skill to select IgG1 antibodies based on their strong ability to bind to antigens. See especially pp. 22 – 23. However Adair does not teach administration of antibodies that bind to Aβ protein as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of administering antibodies which bind to Aβ protein for treatment of bleeding taught by Anderson to specifically include the antibodies of IgG1 isotype taught by Kuby and Adair. The motivation to do so would be to select antibodies that bind tightly to the target antigen; this motivation flows directly from the prior art references themselves. Anderson teaches that the treatment with antibodies is efficacious; Adair teaches that antibodies of IgG1 isotype bind to antigens very well, and Kuby teaches that the biological properties of the specific isotypes is dependent upon the structure of the constant region, not the variable (antigen-binding) domain.

Although Anderson does not explicitly teach selection of a human monoclonal antibody of isotype IgG1 as encompassed by claim 88, doing so would be obvious to the artisan of ordinary skill. Selecting a human monoclonal antibody would be advantageous, as this antibody would elicit a decreased immune reaction, particularly as compared to a mouse antibody. Note that Anderson specifically teaches humanized antibodies and the need to humanize antibodies in order to decrease immune response (column 12 line 10). Thus selecting a human monoclonal antibody of isotype IgG1 would have been obvious to one of ordinary skill in the art, particularly in light of the Anderson reference which teaches the need to minimize immune rejection and teaches administration to humans.

It would have been obvious to one of ordinary skill in the art to modify the method of Anderson by adjusting the dose (claims 95 – 96) or duration (claim 101) of the administration protocol, with a reasonable expectation of success. The motivation to do so would be to more effectively treat hemorrhaging conditions. See MPEP § 2144.05(II), which states that optimization of conditions through routine experimentation is not considered a contribution over the prior art and thus rejections under 35 USC § 103 are appropriate.

On p. 14 of the remarks filed 16 April 2007, applicant argues that "any allegation in the next office action that rejection of these claims [claims 10 and 88] was necessitated by applicant's amendment would be incorrect", as the only reasonable interpretation of claim 88 was that it limited the method of administering antibodies of claim 1 to human monoclonal antibodies of isotype IgG1. Applicant argues that since claim 82, prior to this amendment, read "...or a human monoclonal antibody and the antibody is of isotype human IgG1", claim 88 necessarily limited claim 82 to administration of human monoclonal IgG1 antibodies, and that this limitation was not addressed by the examiner in the previous office action. Applicant's arguments have been fully considered but they are not persuasive. Claim 82, as previously

presented, was very confusing. It was unclear whether the limitation "the antibody is of isotype human IgG1" referred to "a human monoclonal antibody" which immediately preceded such language or to "wherein the antibody is a chimeric or humanized antibody", which occurred earlier but used the same definite article. The recitation "the antibody" lacked definite antecedent basis as there were multiple recitations of "antibody" at various points in the claim before the recitation of "the antibody". As claim 82 now very clearly requires that any of the antibodies administered be human IgG1 isotype, the inclusion of claim 88 in this rejection was in fact necessitated by applicant's amendment.

22. Claims 82 – 84, 87 – 90, 95 – 99, and 100 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 above, and further in view of Miller (U.S. Patent 5,227,159, of record).

The reasons why the references by Anderson, Kuby, and Adair render obvious claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 are set forth above. However none of the references explicitly teaches monitoring the patient for antibody levels as recited in claim 100.

Miller teaches administration of anti-HIV antibodies for treatment of disease. Miller also teaches measuring the levels of antibodies and repeating administration of the antibody as indicated by the circulating antibody levels (see column 15 lines 52 - 62), which is on point to claim 100. However Miller does not teach administration of antibodies which bind Aβ.

It would have been obvious to monitor antibody levels as taught by Miller, following administration as taught by Anderson. The motivation to do so would be to optimize the circulating level of antibody, thereby ensuring that the appropriate dose was maintained.

23. Claims 82 – 90, 95 – 99, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 above, and further in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342).

The reasons why the references by Anderson, Kuby, and Adair render obvious claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 are set forth above. However none of the references explicitly teaches administering to patients under 50, as recited in claim 85, or patients with inherited risk factors as recited in claim 86.

Brookmeyer teaches that the incidence of Alzheimer's disease increases as people age, and further teaches that delaying onset or reducing severity even slightly would result in enormous savings, given the expected financial burden of the disease and the increasing percentage of the population that will live to old age. However Brookmeyer does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to use the method of Anderson to treat patients under 50, or patients either with or without known risk factors, with a reasonable expectation of success. The motivation to do so would be to delay the onset of the disease, which would result in considerable savings.

24. Claims 82 – 84, 87 – 90, 93, 95 – 99, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 above, and further in view of Yachi (EP 0 285 159, published 10 May 1988).

The reasons why the references by Anderson, Kuby, and Adair render obvious claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 are set forth above. However none of these references explicitly teaches administering a second antibody that binds to amyloid deposit as recited in claim 93.

Yachi teaches a second antibody that binds to Aβ protein. However Yachi does not teach administration for prophylaxis of disease.

It would have been obvious to one of ordinary skill in the art to co-administer the antibodies from Anderson and Yachi, with a reasonable expectation of success. It is *prima facie* obvious to co-administer two compounds known to be suitable for the same purpose (MPEP § 2144). Anderson and Yachi teach antibodies that bind Aβ, and Anderson teaches they are suitable to be administered to patients for treatment of stroke.

25. Claims 82 – 84, 87 – 90, 94 – 99, and 101 – 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 above, and further in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

The reasons why the references by Anderson, Kuby, and Adair render obvious claims 82 – 84, 87 – 90, 95 – 99, and 101 – 102 are set forth above. Anderson teaches that when

antibodies are administered to patients they can be labeled (column 13) and after such administration biological samples can be withdrawn and assayed for the presence of Aβ by detecting the antibodies. However none of these references explicitly teaches heterologous peptides fused to the antibodies as recited in claim 94.

Zhang et al. teach labeling by epitope-tagging for detection of molecules. It would have been obvious to one of ordinary skill in the art to epitope tag the antibody of Anderson, as taught by Zhang et al., with a reasonable expectation of success. A motivation to do so would be to detect the antibody in a heterogeneous sample. Anderson teaches that their antibodies are useful for detection following administration to a patient. Because these are heterogenous samples using a labeled antibody as taught by Zhang is particularly useful, as the epitope allows for easy detection.

Conclusion

26. No claim is allowed.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
July 5, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER